REMARKS

I. Status of the claims

Claims 86, 94-98, 100-102, 110-111, and 114-119 are pending and under examination. Claims 1-85, 87-93, 99, 103-109 and 112-113 remained cancelled without prejudice. No claims have been amended in this response.

II. Rejection of claims 86, 94-98, 100-102, 110-111, and 114-119 under 35 U.S.C. § 112

Claims 86, 94-98, 100-102, 110-111, and 114-119 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The examiner states that Applicants have not shown possession of the entire claimed genus of lipophilic groups having a logKow exceeding 1 wherein the group is attached to a dsRNA and binds a (+) strand RNA and has the function of increased lipophilic properties.

The examiner contends that Applicants "cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated," and that Applicants "will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when … the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." See Office Action mailed July 30, 2010, page 6.

The concept of log K_{ow}, however, is well known to one skilled in the art and the log K_{ow} value of a compound can be well predicted using methods known in the art. See, e.g., Sangster, "Octanol-Water Partition Coefficients: Fundamentals and Physical Chemistry," Vol. 2 of Wiley Series in Solution Chemistry, Chichester: John Wiley & Sons Ltd., 1997. Applicants direct the examiner's attention to paragraph 2 on page 13 of the specification, which describes the definition of log K_{ow}, a method to measure or predict values of log K_{ow} and provides the predicted log K_{ow} values for certain exemplified compounds. In the specification, Applicants also refer to a reference (Tetko et al., "Prediction of n-Octanol/water partition coefficients from PHYSPROP data base using artificial neural networks and e-state indices" J. Chem. Inf. Comput. Sci., 2001, 41:1407-21) that describes the principles and methods of predicting values of log K_{ow} given a molecule's chemical formula. Thus where an experimental determination is not feasible,

such methods described in the reference can readily be employed by one skilled in the art to predict the log K_{ow} of a compound. See, e.g., lines 22-25 on page 13 of the specification.

In view of the supporting specification, one skilled in the art would understand how one can determine or predict log K_{ow} of a compound and would be able to predict the operability of other species (lipophilic groups) defined by log K_{ow} that exceed 1. Based on these principles, one skilled in the art would be able to determine which compounds fall within the claimed invention and which fall outside the claimed invention. Thus, and in contrast to the examiner's statements, there would be little to no unpredictability in determining what compounds—whether they were exemplified or not—have a log K_{ow} value that exceed 1. Clearly, Applicants have possession of the claimed invention, one part of which relates to a log K_{ow} value that can easily be determined by one skilled in the art based on the specification.

In view of the above remarks, Applicants respectfully request that the examiner withdraw this rejection under 35 U.S.C. § 112, first paragraph.

II. Rejection of claims 86, 94-98, 100-102, 110-111, and 114-119 under 35 U.S.C. § 103

Claims 86, 94-98, 100-102, 110-111, and 114-119 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Application Publication No. 2003/0139363 to Kay et al. ("Kay"), U.S. Patent Application Publication No. 2003/0143732 to Fosnaugh et al. ("Fosnaugh"), the Manoharan article entitled, "Oligonucleotide conjugates as potential antisense drugs with improved uptake, biodistribution, targeted delivery, and mechanism of action" *Antisense & Nucleic Acid Drug Development*, 2002, 12:103-128 ("Manoharan"), the Mackellar et al. article entitled, "Synthesis and physical properties of anti-HIV antisense oligonucleotides bearing terminal lipophilic groups" *Nucleic acid Research*, 1992, 20(13): 3411-3417 ("Mackellar"), and evidenced by Virta article entitled "Solid-supported synthesis of oligomeric bioconjugates" *Tetrahedron*, 2003, 59:5137-5174 ("Virta").

The examiner maintains applying Kay for the teaching of dsRNA that efficiently inhibit viral gene expression, and targeting hepatocyte cells using a dsRNA molecule capable of inhibiting the expression of a Hepatitic C Virus. See Office Action mailed July 30, 2010, page 8. Kay does not teach, nor is Kay cited for the teaching of a lipophilic group linked at the 5' end of the antisense strand of dsRNA with a phosphodiester group, as required by the pending claims.

The examiner also maintains the citation of Fosnaugh for teaching a dsRNA that comprises a conjugate covalently attached to the dsRNA, with broad language suggesting that the conjugate may be attached to either end of either strand. By additionally citing Manoharan, Mackellar and Virta, the examiner allegedly provides the motivation of attaching a lipophilic group to the 5' end of the antisense strand of a dsRNA. Manoharan is cited by the examiner as disclosing that conjugation of cholesterol to the 5' end of an antisense molecule presents better serum stability and is more efficient at reducing target gene expression *in vivo*. See Office Action mailed July 30, 2010, pages 9-10. Mackeller allegedly discloses that the benefits of attaching a cholesterol moiety to the 5' end of an oligonucleotide were well known in the art. See Office Action mailed July 30, 2010, page 9. Virta is also cited as teaching that attaching conjugates to the 5' end is a simpler process than the 3' end. See Office Action mailed July 30, 2010, pages 9-11. Additionally, the examiner continues to rely on Fosnaugh for teaching that the conjugate can be linked with biodegradable linkers and phosphodiester linkages. See Office Action mailed July 30, 2010, page 8. Applicants respectfully traverse this rejection.

Kay, as acknowledged by the examiner in the Office Action, does not teach a lipophilic group linked at the 5' end of the antisense strand of a dsRNA with a phosphodiester group as required by the pending claims. See Office Action mailed July 30, 2010, page 8.

Fosnaugh is cited, and is the only reference cited, for the proposition that the conjugate can be attached through known biodegradable linkers, including phosphodiester linkages. However, as Applicants noted in the previous responses, Fosnaugh provides too many alternatives that one skilled in the art could easily pursue besides those identified by the examiner, and the examiner has not presented any rationale for showing how one of ordinary skill in the art would navigate through each possible linker disclosed by Fosnaugh, incorporating the alternatives that would work while disregarding those that would not work. Fosnaugh itself certainly provides no guidance on why certain linkages should be utilized in conjugation through the 5' end of antisense strand of the dsRNA. See pages 8-9 of the Response filed February 12, 2010 and pages 6-8 of the Appeal Brief filed May 21, 2010.

Fosnaugh is also cited as disclosing conjugation through the 5' end of the antisense strand. However, Fosnaugh was simply stating that the conjugates disclosed in this reference (not the conjugates recited in Applicants' claimed invention) can be attached at one of the ends

of the strand. Again, as Applicants noted in the previous responses, when taking into account the full disclosure of Fosnaugh, it becomes clear that there are numerous possibilities disclosed within the reference (or generally known by one of ordinary skill in the art) for choosing different conjugates and different ways to attach the conjugate to the dsRNA. However, there is no direction given why one skilled in the art would pursue the path identified by the examiner rather than the many other disclosed alternatives. See *Ortho-McNeil Pharm., Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358 (Fed. Cir. 2008). In *Ortho-McNeil*, the Court stated that one of ordinary skill in the art would have to have some reason to select (among several unpredictable alternatives) the route that would ultimately lead to the claimed invention. 520 F.3d at 1364. The challenges of the inventive process would have prevented one of ordinary skill from traversing the multiple obstacles and arriving at the claimed invention. *Id.* at 1365. In this case, like *Ortho-McNeil*, one of ordinary skill in the art would have to have a rationale for selecting the particular route, amid unpredictable alternatives, that would have lead to the claimed invention.

To cure the deficiencies of Kay and Fosnaugh, the examiner then contends that the motivation of attaching a lipophilic group to the 5' end of the antisense strand of a dsRNA is provided by Manoharan, Mackellar and Virta. However, Applicants respectfully submit that none of the references provide one skilled in the art with the requisite motivation to conjugate a lipophilic group to the 5' end of the antisense strand of a dsRNA through a phosphodiester linkage.

With respect to the examiner's assertion in Manoharan that "the 5' cholesterol conjugated oligonucleotide was more effective at reducing target gene expression *in vivo*," the full passage clearly shows that the better efficacy was based on the comparison <u>between the 5' end conjugated and the unconjugated</u> oligonucleotide, not the comparison between the <u>5' end conjugated and the 3' end conjugated</u> oligonucleotide. Thus this citation from Manoharan cannot be used as a motivation for one skilled in the art to attach conjugates to the 5' end rather than the 3' end.

The examiner also cites a passage in Manoharan stating that the authors "found the 5' cholesterol conjugated … had a plasma half life … greater than the 3' cholesterol conjugated oligonucleotide." However, this too is not supported by a full reading of Manoharan. See pages

107-109 of Manoharan, in particularly, the example on page 107, left column and the example on page 109, left column. The first example shows that a 3'-end cholesterol conjugation to an antisense was more active than the 5' end (page 107, left column); and the second example demonstrates that the 5'- cholesterol conjugated oligonucleotide did not present enhanced resistance to metabolism as compared to the unconjugated oligonucleotide, while the 3' cholesterol conjugated oligonucleotide was more stable than the 5' end conjugated and the unconjugated oligonucleotide (page 109, left column). Therefore, a complete reading of Manoharan suggests that, contrary to the examiner's assertions, the 5' end conjugation is <u>not</u> more stable and more active than the 3' end conjugation for an antisense oligonucleotide. Hence Manoharan cannot be relied upon as providing the motivation to attach a lipophilic group to the 5' end of the antisense rather than the 3' end through a phosphodiester, or otherwise cure the deficiencies of Kay and Fosnaugh, identified above.

With respect to Mackeller, the examiner alleges that "the benefits of attaching a cholesterol moiety to the 5' end of an oligonucleotide were well known in the art." See Office Action mailed July 30, 2010, page 9. However, Mackeller merely discloses that a lipophilic group can be covalently attached to either the 5' or the 3' termini of oligonuceotides. See Mackeller, "Conclusion" on page 3413. Mackeller provides no rationale whether the lipophilic group should be attached to the 5' end or the 3' end. Further, Mackeller fails to teach or suggest the lipophilic conjugation method to an antisense strand in <u>a dsRNA agent</u>. Similarly, Virta, directed to a general synthetic strategy of oligonucleotide conjugation, also fails to teach or suggest the lipophilic conjugation method to an antisense strand in a dsRNA agent. Mackellar and Virta together disclose nothing more than the general synthetic strategy of conjugation to an oligonucleotide. These two references <u>are completely silent on the gene silencing activity</u> of the conjugated oligonucleotide, much less a comparison of the activity of dsRNA containing a conjugation on either the sense strand or the antisense strand, or on either end of the strand. Without this, or some other relevant teaching that would motivate one skilled in the art to choose the 5' end of the antisense strand of a dsRNA, the references provide little value. Accordingly, Mackellar and Virta, like Manoharan, fail to provide one skilled in the art with the requisite motivation to conjugate at the 5' end of the antisense rather than the 3' end through a phosphodiester, or otherwise cure the deficiencies of Kay and Fosnaugh, identified above.

Expectation of success

At the time of the invention, those of ordinary skill in the art understood that there were clear differences for conjugation strategies in general synthesis of oligonucleotide, antisense technology and dsRNA technology; and that there were clearly different structural features of nucleic acids required for activity in each, for example, dsRNA, antisense and aptamer technologies, because the mechanism of action of these nucleic acids differed in each. At the time of the invention, the mechanism of dsRNA had not yet been explored to the extent that one of ordinary skill in the art understood or could predict the effect of a conjugation in a strand on gene silencing activity of the dsRNA.

Applicants clearly point out in the specification that "<u>[D]espite efforts in increasing the efficiency of antisense technology</u>, particularly by enhancing uptake of antisense oligonucleotides by cells, <u>there is currently no known means for improving the efficiency of RNA interference by dsRNA</u>. Thus, there remains a need for a more effective dsRNA molecule that can selectively and efficiently silence a target gene... ." Just because Manoharan teaches a conjugation method to an antisense oligonucleotide in an antisense technology does not mean the same technology would be applicable for a dsRNA to show stability and gene silencing activity. Likewise, just because Mackellar and Virta teach the synthetic strategy of conjugation to an oligonucleotide or an antisense does not mean the same strategy could be used to conjugate an antisense strand in the dsRNA, much less conjugate to a dsRNA in a manner that would have made the oligonucleotide stable and possess gene silencing activity.

Moreover, <u>irrespective the teachings in the antisense technology,</u> at the time of the invention, the art of RNA interference as a whole would have steered one skilled in the art away from proceeding in the manner chosen by Applicants. Based on the art of RNA interference at the time of the invention, one skilled in the art would have expected that a dsRNA with 5' end modifications in the antisense strand, regardless the type of the conjugates, is unable to cause RNA interference.

As disclosed in the specification and discussed in previous responses, various references have shown that the 5' end phosphodiester modification of an antisense strand of a dsRNA completely abolished its activity or at least reduced its activity compared to a dsRNA with an unmodified antisense strand, largely because blocking the 5'-OH of the antisense strand inhibited

the ability of a siRNA to interfere with the expression of its target gene. As known to one skilled in the art of RNA interference at the time of the invention, the 5' OH of the antisense strand of an siRNA was believed to be important and necessary for RNAi activity, because *in vivo* kinase was considered a required process for RNAi activity; an antisense strand, if the 5' OH is blocked, cannot be further phosphorylated by kinase *in vivo*. Thus, taking together all teachings in the art of RNA interference, one skilled in the art would not have been motivated to modify the 5'-OH of the antisense strand with the expectation that the dsRNA could enable RNAi interference. See pages 2-3 of the specification, pages 6-7 of the Response filed February 12, 2010 and page 6 of the Appeal Brief filed May 21, 2010. One skilled in the art would not ignore the clear teachings of these references and attempt conjugation of a phosphodiester linker through the 5' end of the antisense strand of the dsRNA with any expectation of success.

Indeed, in view of the art as a whole, one would have no reasonable expectation of success of successfully preparing the claimed invention in view of the art-recognized failures in this area. In fact, it was not until this invention that the inventors recognized that a highly lipophilic group can be conjugated on the 5' end of the antisense strand of a dsRNA through the use of a phosphodiester linkage while still maintaining or even improving the biological activity and RNA interference activity of the dsRNA.

Unexpected results

In the Office Action mailed July 30, 2010, the examiner responds to Applicants arguments relating to the unexpected results, stating that the results are what have been shown in the prior art and what is expected when conjugating a cholesterol group to the 5' end of an oligonucleotide. See Office Action mailed July 30, 2010, page 14. Applicants respectfully disagree with the examiner's assertion.

As Applicants have discussed above, one skilled in the art would not have expected, before this invention, that dsRNA with 5' end modifications in the antisense strand would cause RNA interference. Yet despite this, Applicants have surprisingly discovered that covalently linking a highly lipophilic group through a phosphodiester linker to the 5' end of the antisense strand of a dsRNA <u>is actually stable and maintains or even improves the RNA interference</u>

activity and the biological activity of the dsRNA compared to the unconjugated control. See specification, pages 32-33 and Fig. 3, as well as the Appeal Brief filed May 21, 2010.

In Fig. 3, Applicants provide various compounds conjugated with highly lipophilic groups. Four of these compounds, HCVC32-as, GalC32-as, HCVChol-as, and GalChol-as, illustrate examples of lipophilic groups covalently attached to a 5' end of the antisense strand of a dsRNA through a phosphodiester linker. See pages 32-33 of the specification. The lipophilic group cholesteryl (6-hyroxyhexyl) carbamate ("Chol") and 12-hydroxydodecanoic acid bisdecylamide ("C32") are specifically recited in claim 97. Fig. 3 demonstrates that dsRNA of the claimed invention, i.e. having one lipophilic group having a $\log K_{ow}$ exceeding one where the lipophilic group is covalently attached to the 5' end of the antisense strand and where the RNA strand contains a phosphodiester group, achieve an approximate 10-20% reduction in gene expression. Applicants use these results as examples to demonstrate the unexpected advantages exhibited by the claimed dsRNA having an antisense strand covalently linked to lipophilic groups through a phosphodiester linker.

The examiner also acknowledges that "Figure 3 does in fact show a dsRNA of the claimed invention having a cholesterol attached at the 5' end [of an antisense strand] and shows what appears to be a reduction of expression of a B-gal gene up to 20% as compared to the [unconjugated] control." However, the examiner contends that the same conjugation at the 3' end showed an even greater reduction in gene expression as compared to the control and thus the results are not unexpected because "the evidence does not support the arguments that conjugation of cholesterol at the 5' end allows the dsRNA to have increased uptake and unexpected results as compared to a dsRNA molecule with a conjugate at the 3' end." See Office Action, page 14.

Applicants respectfully disagree with the examiner's conclusion. As shown in the specification as well as in various references in the art at the time of the invention, the 5' end phosphodiester modification of an antisense strand of a dsRNA of a lipophilic group completely abolished, or at least reduced, its activity compared to an unmodified antisense strand, because blocking the 5'-OH of the antisense strand inhibited the ability of a siRNA to interfere with the expression of its target gene. Therefore, what is unexpected and surprising is that conjugation of a lipophilic group to the 5' end of an antisense strand through a phosphodiester modification of a

dsRNA would actually enable or even improve the RNA interference activity and the biological activity of the dsRNA. This discovery itself is surprising and unexpected in view of what has been presented in the relevant prior art references.

In sum, it is clear that Kay, Fosnaugh, Manoharan, Mackellar and Virta, taken alone or combined together, fail to teach or suggest Applicants' claimed invention. Accordingly, Applicants respectfully request that the examiner withdraw this rejection under § 103.

V. Conclusion

In view of the above remarks, Applicants respectfully request reconsideration of this application.

Except for issue fees payable under 37 C.F.R. §1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 19-2380. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. §1.136(a)(3).

Respectfully submitted,

/Jeffrey N. Townes, Reg. No. 47,142/
Jeffrey N. Townes
Reg. No. 47,142

Dated: November 1, 2010

Customer No. 84717
NIXON PEABODY LLP
Suite 900, 401 9th Street, N.W.
Washington, D.C. 20004-2128
202.585.8000